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Reactivity of 2-methylene-1,3-dicarbonyl compounds: catalytic enantioselective Diels–Alder reaction

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Abstract—The catalytic enantioselective Diels–Alder reaction of 1,1-dicarbonylethenes **3** with cyclopentadiene in the presence of Ti-TADDOLs, Mg–Ph-box and Mg–Ph-mox complexes was investigated. Although both *exo*- and enantioselectivity with Ti-TADDOL catalysts were poor, they were much improved using Mg–Ph-box or Mg–Ph-mox complexes as chiral catalysts. Thus, **3** was an efficient two-point binding dienophile and the non-C_2-symmetric Ph-mox **8** could be used as a chiral ligand.

1. Introduction

Recently, a great deal of effort has been devoted to the development of catalytic enantioselective Diels–Alder reactions.[1] C_2-Symmetric ligands, such as tetraaryldioxolanedimethanols (TADDOLs)[2] and bis(oxazolines) (boxes),[3] and metal complexes have been proven to be excellent catalysts in the reaction. In most cases 3-alkenoyl derivatives of 1,3-oxazolidine-2-ones have been used as two-point binding dienophiles. The previous report[4] from this laboratory described the Lewis acid-catalyzed diastereoselective Diels–Alder reaction using (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl-2-benzoylacrylate **1** as a dienophile. This report has demonstrated that the reaction proceeds via a two-point binding transition state **2** in which the π-stacking of the chelated conjugated system and benzene ring of the phenylmenthyl group restricts the attack of the diene from the back side, and steric hindrance from the benzoyl moiety blocks the approach of the diene to the benzoyl group because the benzene ring is situated perpendicular to the conjugated enedione system. From these results it was anticipated that the enantioselective reaction would be achieved from the reaction of 1,1-dicarbonylethene **3**, whose two carbonyl groups are different, with cyclopentadiene in the presence of a chiral Lewis acid to produce the chiral Diels–Alder adduct **4**. Ethyl 2-benzoylacrylate **3a**[5] and 1-phenyl-2-methylenebutane-1,3-dione **3b**[5] were chosen as dienophiles and TADDOLs **5** and Ph-box **6** as chiral ligands (Chart 1).

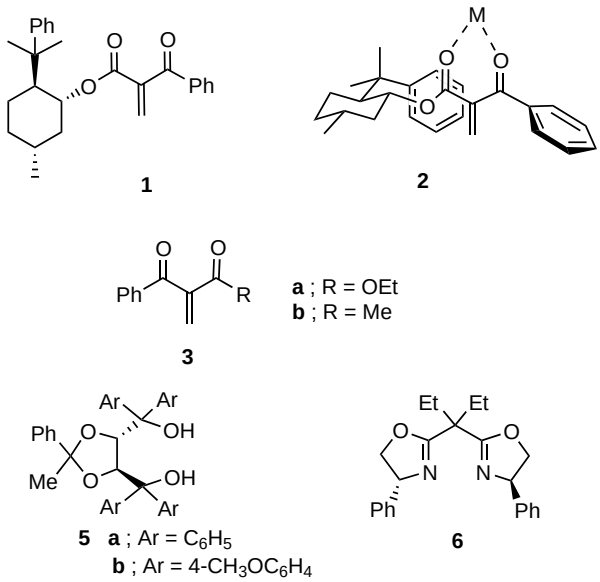

Chart 1.

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2. Results and discussion

Our initial efforts were focused on the possibility that ethyl 2-benzoylacrylate **3a** should be a good two-point binding dienophile in an enantiomeric Diels–Alder reaction.

First the reactions were carried out with TADDOL–titanium combination. The catalysts were prepared according to Narasaka's procedure.[2b] As can be seen from Table 1, reducing the temperature of the reaction has almost no effect on the *exo–endo* (**4a–x**:**4a–n**)[6] ratio or on the enantioselectivity with both **5a** and **5b** ligands, and both the *exo*-selectivities and enantioselectivities were moderate and poor (Scheme 1). Since all of the *exo*-products separated by preparative HPLC are levorotatory, the quaternary carbon of the predominant *exo*-adduct has *S*-configuration (vide infra).

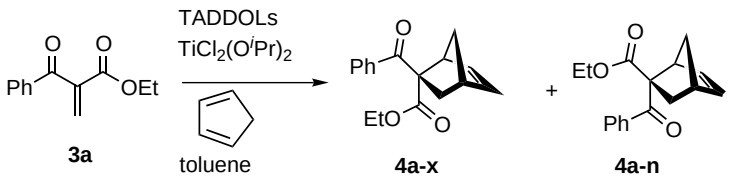
Next oxazoline–magnesium combinations were examined. The reactions were carried out as follows. The catalyst was prepared under the conditions shown in Table 2. The solvent was removed and the resulting complex was dissolved in CH_2Cl_2 and cooled to the requisite temperature. To this solution enedione **3a** or **3b** was added and then cyclopentadiene was added slowly to the mixture (Scheme 2).

In order to test for temperature dependency, the reactions were carried out with the catalyst prepared from 3,3-bis(4-phenyl-4,5-dihydrooxazol-2-yl)pentane (Ph-box) **6**, MgI_2 and I_2 in CH_3CN. Lowering the temperature from −15 to −90°C provided product with significantly improved enantioselectivity (entries 2–4). In the reaction with the complex prepared from **6**, MgI_2 and I_2 in CH_2Cl_2 at room temperature using Corey's procedure,[3c] the enantioselectivity was somewhat inferior to that in CH_3CN (entries 1 and 4). However, both *exo*-selectivity and enantioselectivity were much improved with the complex prepared in refluxing CH_3CN (entry 5). The diastereoisomers produced were chromatographically homogeneous in TLC and could not be resolved by column or medium pressure chromatography, however, the diastereomeric ratio could be determined from the ^1H NMR spectrum, as mentioned in our previous report (Scheme 3).[4]

As **3a** proved to be a suitable dienophile, we next examined the reaction using *N*-[(1*R*)-2-chloro-1-phenylethyl]-2-ethyl-2-[(4*R*)-4-phenyl-4,5-dihydrooxazol-2-yl]butyramide (Ph-mox) **8** as a chiral ligand. Ligand **8** was synthesized by treatment of the dichloride **7** (which was prepared from 2,2-diethyl-*N*,*N*′-bis-[(1*R*)-2-hydroxy-1-phenylethyl)-malonamide)[7] with an equimolar amount of NaOH in MeOH–H_2O at 60°C. Ligand **8** exists as colorless prisms (mp 127–128°C from ethyl acetate). The reaction using the complex prepared from **8**:MgI_2:I_2 (1:1:1) in CH_2Cl_2 at room temperature also gave poor enantioselectivity (entry 6). However, when the reaction was performed with the same complex prepared in refluxing CH_3CN, the e.e. of product increased to 87% (entry 8). Interestingly, the enantioselectivities of reactions with the complex prepared from MgI_2:**8**:I_2 (1:2:2) (half amounts of Lewis acid compared with entry 7) were almost equal or slightly higher (entry 9). All *exo*-products obtained with **6** and **8** were dextrorotatory, and enantioselectivities were determined by analytical HPLC. In order to confirm the absolute configuration, enantiomerically pure **4a–x**, obtained by recrystallization of the *exo*-product (entry 9), was treated with bromine in CCl_4. The product showed carbonyl absorptions at 1786 and 1674 cm^{-1} in the IR spectrum and its ^1H NMR spectral pattern was very similar to that[8] of 9-bromo-5-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-4-one. X-Ray crystallographic analysis[9] shows that the product has the structure **9** and therefore the quaternary carbon of the Diels–Alder adduct **4a–x** is *R*-configured. Since the Ph-mox **8** was recovered almost

Table 1. Enantioselective Diels–Alder reaction of **3a** with cyclopentadiene using TADDOLs **5a** and **5b** as Lewis acid catalysts

Entry	Ligand	*T* (°C)	Yield (%)	**4a–x**:**4a–n**	% e.e. of **4a–x**
1	**5a**	0	65	82:18	24
2	**5a**	−40	69	85:15	22
3	**5a**	−80	61	86:14	18
4	**5b**	0	72	86:14	16
5	**5b**	−15	65	87:13	24
6	**5b**	−40	62	85:15	24

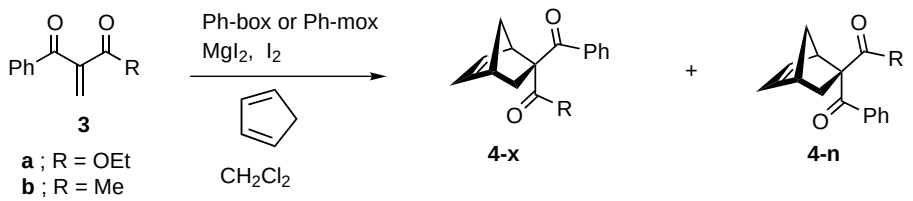


Scheme 1.

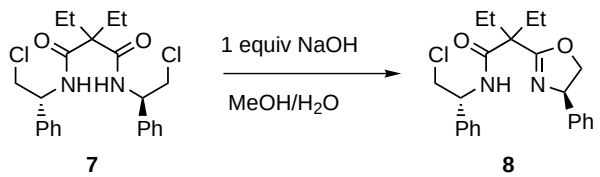
Table 2. Enantioselective Diels–Alder reaction of **3a** and **3b** with cyclopentadiene using Ph-box **6** and Ph-mox **8** as chiral ligands

Entry	R	Catalyst				Reaction conditions			Product	
		Ligand (equiv.)	MgI_2 (equiv.)	I_2 (equiv.)	Conditions	T (°C)	t (h)	Yield (%)	**4–x**: **4–n**[a]	% e.e. of **4x**[b]
1	OEt	**6** (0.2)	0.2	0.2	CH_2Cl_2, rt, 3 h	−90	6	74	97:3	70
2	OEt	**6** (0.2)	0.2	0.2	CH_3CN, rt, 1 h	−15	2	70	96:4	18
3	OEt	**6** (0.2)	0.2	0.2	CH_3CN, rt, 1 h	−50	4	76	98:4	42
4	OEt	**6** (0.2)	0.2	0.2	CH_3CN, rt, 1 h	−90	7	75	98:2	78
5	OEt	**6** (0.2)	0.2	0.2	CH_3CN, reflux, 1 h	−90	6	81	>99:1	85
6	OEt	**8** (0.2)	0.2	0.2	CH_2Cl_2, rt, 3 h	−90	6	76	>99:1	18
7	OEt	**8** (0.2)	0.2	0.2	CH_3CN, reflux, 1 h	−90	6	88	>99:1	87
8	OEt	**8** (0.2)	0.1	0.2	CH_3CN, reflux, 1 h	−90	8	88	>99:1	87
9	OEt	**8** (0.4)	0.2	0.4	CH_3CN, reflux, 1 h	−90	8	75	>99:1	89
10	Me	**6** (0.2)	0.2	0.2	CH_3CN, reflux, 1 h	−90	12	77	98:2	78
11	Me	**8** (0.2)	0.2	0.2	CH_3CN, reflux, 1 h	−90	15	84	97:3	69
12	Me	**8** (0.2)	0.1	0.2	CH_3CN, reflux, 1 h	−90	21	78	97:3	81

[a] Ratios were determined by ^1H NMR (olefinic protons).
[b] % e.e. was determined by HPLC using a Chiralcel OD column.



Scheme 2.

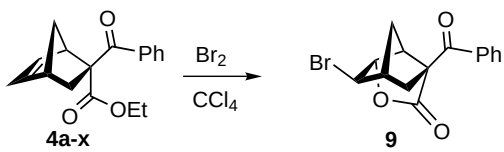


Scheme 3.

quantitatively from column chromatography after the reaction, the possibility of conversion of Ph-mox **8** into Ph-box **6** during the preparation of the chiral catalyst or the reaction was eliminated (Scheme 4).

The reaction of 1-phenyl-2-methylenebutane-1,3-dione **3b** was also examined. All reactions were carried out at –90°C, with the catalyst prepared previously in refluxing CH_3CN. The reactions gave products with enantioselectivities of up to 81%. Both the *exo*-selectivity and enantioselectivity were lower than those in the case of **3a**, which might be due to steric hindrance from the methyl group which is larger than the oxygen of the ethoxy group in the fixed transition state.

As mentioned earlier, the observed high diastereoselectivity can be rationalised as being due to the steric hindrance from the benzene ring situated nearly perpendicular to the ene in the fixed metal-chelated enedione.[4] The sense of the asymmetric induction in the reaction with Ph-box **6** can be rationalized by assuming that the reaction proceeds via the intermediacy of a square-planar **10**[3d] or an octahedral **11**[3g] rather than a tetrahedral **12**[3c] complex. Both the square-planar and the octahedral models predict that cyclopentadiene should approach to the *re* face in the case of **3a** and to the *si* face in the case of **3b** of a chelated dienophile. Whereas the tetrahedral model predicts that cyclopentadiene approaches from the opposite face (if the reaction take place). Another possibility that the reaction might not occur in the tetrahedral model is not neglected because both phenyl groups hinder cyclopentadiene from approaching to the both sides. In the case of Ph-mox **8** as a ligand somewhat C_2-symmetric-like transition state must also be taken into account. In order to resolve this problem we obtained the ^1H NMR spectra of complexes prepared from equimolar amounts of Lewis acid and chiral ligand. In the ^1H NMR spectrum of the Ph-mox **8**–Mg complex prepared in refluxing CH_3CN, only one set of signals corresponding



Scheme 4.

to oxazoline ring protons and amide side-chain protons was observed. The signals for the oxazoline ring protons were broadened and observed ca. 0.2 ppm downfield of the corresponding peak for Ph-mox **8**, while the methylene protons of the amide side-chain, which appeared as double AB quartets in the spectrum of **8**, were seen as a broad doublet in **8**–Mg (ca. 0.15 downfield shift) and the methyne proton was slightly broadened (ca. 0.5 ppm downfield shift). On the other hand, in the spectrum of the **8**–Mg complex prepared at room temperature, the signals in the region of 4–6 ppm were complicated. Some of the signals were not identical with those of **8**-Mg complex prepared in refluxing CH_3CN, and of the parent ligand **8**. From these results we concluded that chelation was not complete at room temperature and conformational rigidity was achieved only in the **8**–Mg complex prepared in refluxing CH_3CN. Thus, a plausible transition state is shown as **13** in Fig. 2, in which hydrogen bonding between the chloride and the amide hydrogen plays an important role. PM3 calculations on the **8**–Mg complex reveal that the optimal conformation of the complex has a structure like **13** from which the enedione is omitted.

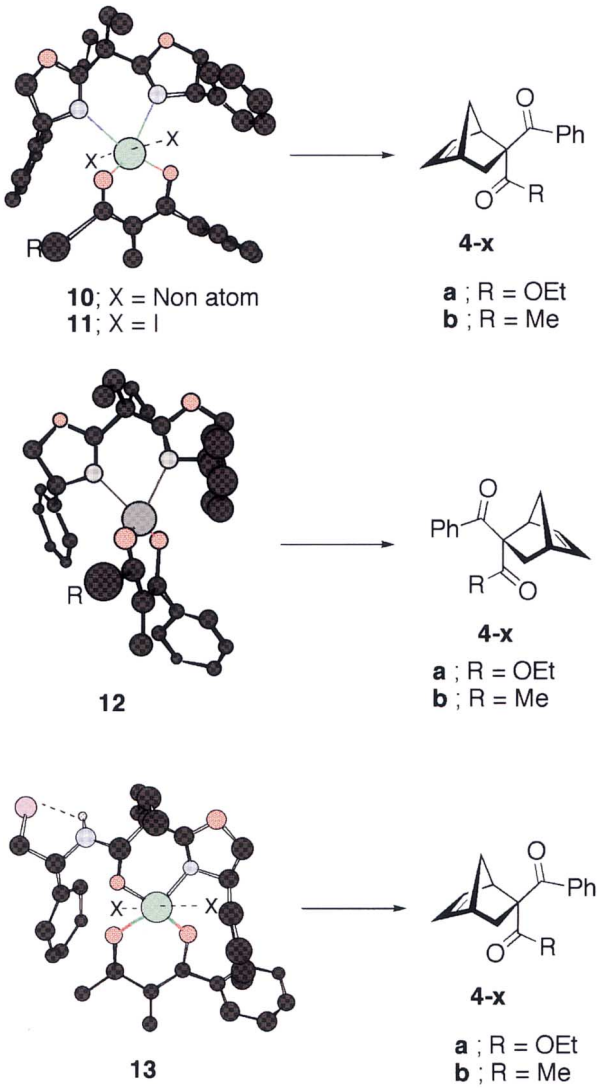


Figure 2.

It was thought that usage of bis(amide) **7** as a chiral ligand may also be possible provided the amide side-chains are fixed in the transition state. In fact the Diels–Alder reaction of **3a** and cyclopentadiene with **7**–Mg complex, prepared in refluxing CH_3CN, gave the *exo*-products **4a**–**x** in ca. 80% e.e., less satisfactory than in the case of **8**.

3. Experimental

3.1. General

Melting points are uncorrected. $MgSO_4$ was used to dry organic layers after extraction. Column chromatography was performed with Silica Gel 60 (Spherical, Kanto Chemical Co.). HPLC was carried out with a Daisel Chiralcel OD column (0.46×25 cm; eluent 0.1% propan-2-ol in hexane). NMR spectra were recorded in chloroform-*d* at 270 MHz for ^1H and 67.89 MHz for ^{13}C NMR using tetramethylsilane as an internal standard. IR spectra were determined either neat or in KBr pellets. High-resolution mass spectra were recorded at 70 eV.

3.2. General procedure for reaction of 3a with titanium–TADDOL complex

Under an argon atmosphere, to a solution of $TiCl_2(O^iPr)_2$ (21.2 mg, 0.098 mmol) in toluene (2 mL) was added a solution of the chiral TADDOL (0.098 mmol) in toluene (2 mL) and 4 Å MS (120 mg) at room temperature, and the mixture was stirred for 1 h, then cooled to the temperature shown in Table 1, and a solution of **3a** (200 mg, 0.98 mmol) in toluene (4 mL) was added. Stirring was continued for 0.5 h and a solution of cyclopentadiene (65 mg, 0.98 mmol) in toluene (5 mL) was added over a period of 2 h. The reaction mixture was stirred overnight at the same temperature, and then pH 7 phosphate buffer (10 mL) was added to the mixture. The organic layer was extracted with ethyl acetate (3×10 mL). The combined extracts were dried and evaporated. The residue was purified by column chromatography to give the Diels–Alder adducts (Table 1).

3.3. *N*,*N*′-Bis[(1*R*)-2-chloro-1-phenylethyl]2,2-diethyl-1,3-propanediamide 7

A solution of *N*,*N*′-bis[(1*R*)-2-hydroxy-1-phenylethyl]-2,2-diethylmalonamide (7.7 g, 22 mmol) in $SOCl_2$ (33 mL, 0.45 mol) was heated under reflux for 4 h. Excess $SOCl_2$ was evaporated and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (50 mL×2) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried and evaporated. The resulting residue was purified by column chromatography ($CHCl_3$) to yield **7** (3.98 g, 91%); mp 157–159°C (from $CHCl_3$), IR 3300, 1640 cm^{-1}; ^1H NMR δ 0.87 (t, J=7.5 Hz, 6H), 1.97 (q, J=7.5 Hz, 4H), 3.79 (dd, J=11.5, 6.1 Hz, 2H), 3.88 (dd, J=11.5, 5.0 Hz, 2H), 5.38 (br t, J=6.3 Hz, 2H), 7.26–7.35 (m, 10H), 7.91 (br d, J=7.5 Hz, 2H); ^{13}C

NMR δ 9.5, 30.9, 47.6, 54.0, 58.4, 126.5, 128.1, 128.8, 138.5, 172.8. $[\alpha]_D^{18}$ −78.0 (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{23}H_{28}N_2O_2Cl_2$: C, 63.45; H, 6.48; N, 6.43. Found: C, 63.29; H, 6.49; N, 6.33%.

3.4. *N*-[(1*R*)-2-Chloro-1-phenylethyl] 2-ethyl-2-[(4*R*)-4-phenyl-4,5-dihydrooxazol-2-yl]butyramide 8

To a solution of **7** (3.104 g, 7.1 mmol) in MeOH (150 mL) was added NaOH (284 mg, 7.1 mmol) in H_2O (40 mL) at 50°C and the reaction mixture was stirred for 1 h at the same temperature. The mixture was concentrated to 1/5 of its original volume and extracted with CH_2Cl_2 (2×20 mL). The organic layer was washed with water (2×10 mL), dried and evaporated. The product was then purified by column chromatography (0.5% acetone in CH_2Cl_2) to give crystalline **8** (2.354 g, 83%) as colorless prisms (from AcOEt); mp 127–128°C; IR 3210, 1660 cm^{-1}; ^1H NMR δ 0.74 (t, J=7.5 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H), 1.85 (q, J=7.5 Hz, 2H), 2.11 (q, J=7.5 Hz, 2H), 3.75 (dd, J=11.2, 6.1 Hz, 1H), 3.84 (dd, J=11.2, 5.1 Hz, 1H), 4.11 (t, J=8.5 Hz, 1H), 4.70 (dd, J=10.0, 8.5 Hz, 1H), 5.38–5.48 (m, 2H), 7.24–7.40 (m, 10H), 10.88 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 9.8, 10.0, 30.9, 31.4, 48.1, 54.3, 54.7, 69.2, 73.7, 126.2, 126.7, 127.6, 128.4, 128.7, 139.0, 141.5, 170.0, 170.9. $[\alpha]_D^{18}$ −15.1 (*c* 1.26, $CHCl_3$). Anal. calcd for $C_{23}H_{27}N_2O_2Cl$: C, 69.25; H, 6.82; N, 7.02. Found: C, 69.20; H, 6.81; N, 6.98%.

3.5. General procedure for the reaction of enedione (3a and 3b) with Ph-box- or Ph-mox–magnesium complex

A mixture of the ligand, MgI_2 and I_2 in the solvent was treated under the conditions shown in Table 2. The solvent was removed and the resulting complex was dissolved in CH_2Cl_2 (4.0 mL) and cooled at −90°C, a solution of **3** (1 mmol) in CH_2Cl_2 (6.0 mL) was added and the resulting mixture was stirred for 30 min, then a solution of cyclopentadiene (1.5 mmol) in CH_2Cl_2 (5.0 mL) was added slowly over a period of 3 h. When the reaction was complete the reaction was quenched with water and washed with 5% aqueous $Na_2S_2O_3$. The organic layer was dried and evaporated. The resulting residue was subjected to column chromatography to yield the adducts. Physical data and spectroscopic data of the enantiomerically pure Diels–Alder adducts **4a**–**x** and **4b**–**x** are shown below.

3.5.1. (1*R*,2*R*,4*R*)-2-Benzoylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid ethyl ester 4a–x. Colorless needles (from hexane); mp 107–109°C; IR 3444, 1735, 1678 cm^{-1}; ^1H NMR δ 0.98 (t, J=7.0 Hz, 3H), 1.53 (m, 2H), 2.01 (dd, J=12.0, 3.5 Hz, 1H), 2.43 (dd, J=12.0, 2.5 Hz, 1H), 2.97 (br s, 1H) 3.67 (br s, 1H), 3.99 (dq, J=7.0, 2.5 Hz, 2H), 5.97 (dd, J=5.5, 3.0 Hz, 1H), 6.40 (dd, J=5.5, 3.0 Hz, 1H), 7.41 (t, J=7.3 Hz, 2H), 7.52 (t, J=7.3 Hz, 1H), 7.93 (d, J=7.3 Hz, 2H); ^{13}C NMR δ 13.8, 36.1, 43.0, 49.7, 50.1, 61.3, 64.0, 128.4, 129.1, 132.5, 132.9, 135.7, 140.5, 172.3, 197.1. $[\alpha]_D^{21}$ +303.0 (*c* 4.38, $CHCl_3$). Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.57; H, 6.71%. HRMS calcd for $C_{17}H_{18}O_3$: 270.1255. Found: 270.1248.

3.5.2. (1*R*,2*S*,4*R*)-1-[2-Benzoylbicyclo[2.2.1]hept-5-ene-2-yl]ethanone 4b–x. Colorless prisms (from petroleum ether); mp 88–89°C; IR 1715, 1672 cm^{-1}; ^1H NMR δ 1.45 (br d, J=8.8 Hz, 1H), 1.57 (br d, J=8.8 Hz, 1H), 1.89 (dd, J=12.0, 3.5 Hz, 1H), 2.03 (s, 3H), 2.59 (dd, J=12.0, 2.5 Hz, 1H), 2.93 (br s, 1H) 3.82 (br s, 1H), 5.89 (dd, J=5.8, 3.0 Hz, 1H), 6.34 (dd, J=5.8, 3.0 Hz, 1H), 7.41 (t, J=7.3 Hz, 2H), 7.52 (t, J=7.3 Hz, 1H), 7.87 (d, J=7.3 Hz, 2H); ^{13}C NMR δ 27.7, 34.3, 43.2, 49.7, 49.9, 73.8, 128.5, 129.6, 131.3, 133.2, 136.0, 140.8, 198.8, 204.3. $[\alpha]_D^{21}$ +546.4 (*c* 3.86, $CHCl_3$). Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71 Found: C, 79.95; H, 6.84%. HRMS calcd for $C_{16}H_{16}O_2$: 240.1150. Found: 240.1148.

3.6. (1*R*,3*R*,6*R*,7*S*)-3-Benzoyl-9-bromo-5-oxatricyclo-[4.2.1.0^{3,7}]nonane-4-one 9

Bromine (160 mg, 1 mmol) was added dropwise into a solution of enantiomerically pure **4a**–**x** (73 mg, 0.27 mmol) in CCl_4 (4 mL) at −8°C (ice-salt bath). Stirring was continued for 1 h at the same temperature and then for a further 2 h at rt. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a 5% $Na_2S_2O_3$ solution (2×10 mL) and brine (10 mL). The organic layer was dried and evaporated. Recrystallization of the residual solid with AcOEt–hexane gave colorless prisms (80 mg, 92%); mp 170–172°C; IR 1786, 1674 cm^{-1}; ^1H NMR δ 1.69 (br d, J=11.9 Hz, 1H), 2.10 (dd, J=13.5, 2.2 Hz, 1H), 2.33 (br d, J=11.9 Hz, 1H), 2.79 (m, 1H), 2.84 (dd, J=13.5, 4.2 Hz, 1H), 3.85 (br d, J=5.2 Hz, 1H), 3.98 (d, J=2.2 Hz, 1H), 5.13 (br d, J=5.2 Hz, 1H), 7.47 (t, J=7.3 Hz, 2H), 7.59 (t, J=7.3 Hz, 1H), 7.90 (d, J=7.3 Hz, 2H); ^{13}C NMR δ 35.0, 38.6, 45.9, 51.3, 53.0, 56.9, 86.6, 128.6, 127.7, 133.7, 134.1, 176.5, 192.8. $[\alpha]_D^{25}$ −107 (*c* 0.35, $CHCl_3$). Anal. calcd for $C_{15}H_{13}O_3Br$: C, 56.10; H, 4.08. Found: C, 56.12; H, 4.15. HRMS calcd for $C_{15}H_{13}O_3Br$: 320.0048. Found: 320.0066.

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